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TRANSMITTAL FORM

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Total Number of Pages in This Submission

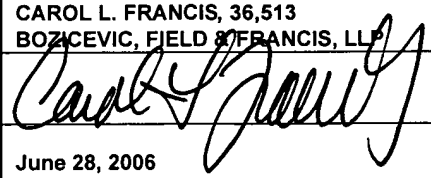
Application Number	**09/509,196**
Filing Date	**March 23, 2000**
First Named Inventor	**DALY, ROGER JOHN**
Group Art Unit	**1649**
Examiner Name	**CHERNYSHEV, OLGA N.**
Attorney Docket Number	**RICE-012**

ENCLOSURES (check all that apply)

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Documents
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
  - ☒ Exhibit to Appellants' Brief: copy of Declaration of Dr. Yasumichi Hitoshi as originally filed on 2-10-03
- ☐ Proprietary Information
- ☒ USPTO Credit Card Form 2038
- ☒ Return postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Signing Attorney/Agent (Reg. No.)	**CAROL L. FRANCIS, 36,513** **BOZICEVIC, FIELD & FRANCIS, LLP**
Signature	
Date	**June 28, 2006**

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APPELLANTS' BRIEF		
Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	RICE-012
	Confirmation No.	8868
	First Named Inventor	DALY, ROGER J.
	Application Number	09/509,196
	Filing Date	March 23, 2000
	Group Art Unit	1649
	Examiner Name	CHERNYSHEV, O.
	Title: "A POTENTIAL EFFECTOR FOR THE GRB7 FAMILY OF SIGNALLING PROTEINS"	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Final Rejection dated February 1, 2006. No claims have been allowed, and Claims 5-7, 19-22, 24-29, and 31-41 are pending. Claims 5-7, 19-22, 24-29, and 31-41 are appealed. A Notice of Appeal was filed on April 28, 2006.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815 to cover any fee required under 37 C.F.R. §1.17(c) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815.

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TABLE OF CONTENTS

REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights in the invention to Garvan Institute of Medical Research. The application is licensed to Rigel Pharmaceuticals.

RELATED APPEALS AND INTERFERENCES

There are no appeals pending which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on March 23, 2000 with Claims 1-15. During prosecution, Claim 16-41 were added and Claims 1-4, 8-18, 23, and 30 were cancelled. Accordingly, Claims 5-7, 19-22, 24-29, and 31-41 are pending in the present application, all of which claims are currently rejected and appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The pending claims are drawn in pertinent part to an isolated polynucleotide molecule comprising a nucleotide sequence having at least 95% sequence identity to a nucleotide sequence encoding SEQ ID NO:2, as well as vectors, transformed host cells, and methods of producing a protein by culturing such transformed host cells. The claimed polynucleotides include: isolated polynucleotides comprising a sequence as shown in SEQ ID NO:1, nucleotides 694-1614 of SEQ ID NO:1, or comprising a sequence having at least 95% sequence identity to SEQ ID NO:1; isolated polynucleotides comprising a sequence encoding an amino acid sequence of SEQ ID

NO:2, or amino acid residues 232-538 of SEQ ID NO:2; isolated polynucleotides comprising a sequence having at least 95% sequence identity to a sequence encoding amino acid residues 232-538 of SEQ ID NO:2; isolated polynucleotides comprising a sequence of nucleotides 694-1614 of SEQ ID NO:1; and isolated polynucleotides comprising a sequence encoding amino acid residues 232-888 of SEQ ID NO:2.

Below is a description of each appealed claim. Where support for each claim can be found in the specification is listed in parentheses, is given as exemplary, and is not intended to be exhaustive. Paragraph and page numbers used below are those appearing in the US Patent Application Publication No. 2002/0037582, published March 28, 2002, for the instant application.

Independent Claim 32 recites an isolated polynucleotide molecule having at least 95% sequence identity to a nucleotide sequence encoding SEQ ID NO:2. (See the specification at paragraph [0007]).

Claim 5 depends from claim 32 and specifies a host cell transformed with the polynucleotide molecule of claim 32. (See the specification at paragraph [0010]).

Claim 6 depends from claim 5 and specifies that the host cell is a mammalian, insect, yeast, or bacterial host cell. (See the specification at paragraph [0010]).

Claim 7 depends from claim 5 and specifies a method of producing a protein, wherein the host cell of claim 5 is cultured under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein. (See the specification at paragraph [0012]).

Claim 19 depends from claim 32 and specifies that the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1. (See the specification at paragraph [0007]).

Claim 20 depends from claim 32 and specifies a vector including a polynucleotide molecule according to claim 32. (See the specification at paragraph [0010]).

Claim 21 depends from claim 20 and specifies that the polynucleotide molecule includes a nucleotide sequence as shown in SEQ ID NO:1. (See the specification at paragraph [0008]).

Independent Claim 22 recites an isolated polynucleotide molecule including a nucleotide sequence having at least 95% sequence identity to that shown in SEQ ID NO:1. (See the specification at paragraph [0007]).

Claim 24 depends from claim 22 and specifies a host cell transformed with the polynucleotide molecule of claim 22. (See the specification at paragraph [0010]).

Claim 25 depends from claim 24 and specifies that the host cell is a mammalian, insect, yeast, or bacterial host cell. (See the specification at paragraph [0010]).

Claim 26 depends from claim 24 and specifies a method of producing a protein, wherein the host cell of claim 24 is cultured under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein. (See the specification at paragraph [0012]).

Claim 27 depends from claim 22 and specifies that the polynucleotide molecule includes a nucleotide sequence as shown in SEQ ID NO:1. (See the specification at paragraph [0008]).

Claim 28 depends from claim 22 and specifies a vector including a polynucleotide molecule according to claim 22. (See the specification at paragraph [0010]).

Claim 29 depends from claim 28 and specifies that the polynucleotide molecule includes a nucleotide sequence as shown in SEQ ID NO:1. (See the specification at paragraph [0008]).

Claim 31 depends from claim 32 and specifies that the polynucleotide molecule includes a nucleotide sequence encoding an amino acid sequence as shown in SEQ ID NO:2. (See the specification at paragraph [0007]).

Independent claim 33 recites an isolated polynucleotide molecule including a nucleotide sequence having at least 95% sequence identity to a nucleotide

sequence encoding amino acid residues 232-538 of SEQ ID NO:2. (See the specification at paragraphs [0007] and [0049] and Figure 1).

Claim 34 depends from claim 33 and specifies a host cell transformed with the polynucleotide molecule of claim 33. (See the specification at paragraph [0010]).

Claim 35 depends from claim 34 and specifies that the host cell is a mammalian, insect, yeast, or bacterial host cell. (See the specification at paragraph [0010]).

Claim 36 depends from claim 34 and specifies a method of producing a polypeptide, wherein the host cell of claim 34 is cultured under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein. (See the specification at paragraph [0012]).

Claim 37 depends from claim 33 and specifies that the nucleotide sequence includes a nucleotide sequence of nucleotides 694-1614 of SEQ ID NO:1. (See the specification at paragraph [0049]).

Claim 38 depends from claim 37 and specifies a vector including a polynucleotide molecule according to claim 33. (See the specification at paragraph [0010]).

Claim 39 depends from claim 38 and specifies a vector including a polynucleotide molecule according to claim 38. (See the specification at paragraph [0010]).

Claim 40 depends from claim 33 and specifies the isolated polynucleotide molecule according to claim 33, wherein the polynucleotide molecule includes a nucleotide sequence encoding amino acid residues 232-538 of SEQ ID NO:2. (See the specification at paragraph [0049] and Figure 1).

Claim 41 depends from claim 33 and specifies the isolated polynucleotide molecule according to claim 33, wherein the polynucleotide molecule includes a nucleotide sequence encoding amino acid residues 232-888 of SEQ ID NO:2. (See the specification at paragraph [0049] and Figure 1).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 5-7, 19-22, 24-29, and 31-41 stand rejected under 35 U.S.C. § 101 as allegedly being drawn to an invention with "no apparent or disclosed specific and substantial credible utility." The quoted phraseology is that employed by the Examiner in the Final Office Action at paragraph 5.

Claims 5-7, 19-22, 24-29, and 31-41 stand further rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement ("how to use") by virtue of the rejection under 35 U.S.C. § 101.

ARGUMENTS

I. In summary, the rejection under 35 U.S.C. § 101 is based on the Examiner's allegation that the claimed invention has "no apparent or disclosed specific and substantial credible utility." Appellants submit that this rejection is flawed both legally and procedurally, and request withdrawal of this rejection.

Legal Flaws in the § 101 Rejection

Appellants' specification discloses at least two utilities for the claimed invention:

1) The claimed polynucleotides are useful in distinguishing cancer cells from normal cells because they are differentially expressed in certain human cancers, e.g., breast and prostate cancer; and

2) The claimed polynucleotides are useful for distinguishing cancer cells from normal cells because they encode a polypeptide (designated 2.2412) that binds to the signaling proteins Grb7 and to Grb14, each of which is known to be differentially expressed in certain cancer cells relative to normal cells. Therefore, because the 2.2412 polypeptide acts as "bait" for Grb7 and Grb14, it is useful as a tumor marker and/or as a prognostic indicator for these cancers.

With regard to the above utilities, Appellants have established in the file record that it was known in the art as of Appellants' filing date that Grb7 and Grb14 are differentially expressed in cancer cells (breast, prostate, gastric, and esophageal cancer) compared to normal cells. Appellants have provided extrinsic evidence that

Grb7 and Grb14 were recognized as markers for cancer at the time of filing of the present application, as well as extrinsic and intrinsic evidence[1] that the 2.2412 polypeptide encoded by the claimed polynucleotide specifically binds to Grb7 and Grb14.

The Examiner dismissed the above evidence by virtue of her position that there is no factual evidence within the instant disclosure regarding differential expression of the polynucleotide encoding 2.2412. She appears to be requiring data showing altered levels or forms of a polynucleotide encoding 2.2412 polypeptide in diseased tissue versus corresponding healthy tissue. She criticized some data published before Appellants' filing date regarding differential expression as "inconclusive." She dismissed other articles published before Appellants' filing date relating to coexpression and coamplification of Grb7 in gastric and esophageal cancers because Appellants' specification does not disclose these types of cancer. She apparently has not considered evidence published after the filing date that supports Appellants' statements of utility.

The Examiner also appears to be confusing a statement of utility, which must be recited in the application as filed, with extrinsic evidence that supports such a statement. The latter evidence in support of a utility statement need not appear in the application as filed. Appellants have cited *In re Hogan*, 194 USPQ 527, 537 (CCPA 1977), which held that later publications that substantiate Applicant's assertions of utility or other art-related facts existing on the filing date are acceptable. The Examiner acknowledged this citation in the Final Office Action, but her only response to this and to all of Appellants' other arguments was a discussion of *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005). Appellants will discuss *Fisher* below.

Appellants have disclosed[2] that the Grb7 family proteins exhibit differential expression in certain human cancers (particularly breast and prostate cancer) (emphasis added). The phrase *certain human cancers* is a generic statement that embraces the gastric and esophageal cancers disclosed by the Kishi *et al.* and Tanaka *et al.* articles, respectively, cited by Appellants in support of their utility

[1] See the specification at, for example, pages 10-11.
[2] See the specification at, for example, page 5.

statement. Apparently the Examiner is requiring that a generic statement of utility be accompanied by an exhaustive litany of specific utilities that fall within the generic utility statement in order for earlier or later published specific knowledge to substantiate Appellants' assertion of utility. This is an unduly burdensome and improper standard.

Appellants submit that the standard used by the Examiner for satisfying the utility requirement is higher than that set forth in the § 101 Guidelines or Training Materials. To satisfy the utility requirement an applicant need only provide one credible assertion of specific and substantial utility for each claimed invention. MPEP § 2107 II(B). Appellants have provided at least two assertions of utility in their specification (see above) that satisfy the utility requirement. If the asserted utility is credible and if it is *more likely than not* that a person of ordinary skill in the art would consider the asserted utility specific and substantial, the utility requirement is met. MPEP § 2107 II(C). This is a preponderance of the evidence standard, a relatively low standard, which is lower than a clear and convincing evidence standard, which itself is lower than a beyond a reasonable doubt standard.

In this regard, extrinsic evidence, especially published before Appellants' filing date, is also evidence of the level of skill in the art. Therefore, Appellants have properly relied upon such evidence to substantiate their utility statement. In addition, because of the evidentiary standard set forth in MPEP § 2107 II(C) (see above), such evidence should be considered by the Examiner in evaluating a utility statement as being credible or specific and substantial. However, the Examiner has dismissed the relevance of the cited extrinsic evidence because she appears to be confusing *assertion* of a utility statement after the filing date (improper) with *substantiation* of an existing utility statement by extrinsic evidence (proper) (see above).

Moreover, by requiring exhaustive data, the Examiner is asking the Appellants to prove their utility statement unequivocally. Thus, the Examiner is applying improperly a standard higher than a preponderance of the evidence standard. In addition, the Examiner has asserted "that the observed overexpression of Grb14 protein in a prostate or breast cell line cannot be unequivocally indicative of Grb14

being a marker for these types of cancer...." September 15, 2005 Office Action at pages 7-8 (emphasis added). This is further evidence that she is employing a standard higher than a preponderance of the evidence standard. Appellants are not required to prove their utility unequivocally.

The burden is on the Office to substantiate any reasons for doubting an asserted utility. Appellants ordinarily submit data only when a *prima facie* case of no specific and substantial utility or no credible utility has been established by the Office. The Examiner has cited only a general paper by Baguley *et al.*. In so doing, once again the Examiner has not met the evidentiary standard of a preponderance of the evidence. The Daly *et al.* paper (J. Biol. Chem. **1996**, *271*:12502-12510) cited previously by Applicant is far more relevant to breast and prostate cancer than is the general Baguley *et al.* paper. Therefore, at best there is a 50-50 tie, pitting Appellants' word against the Examiner's. Because a *tie* does not meet the preponderance of the evidence standard, the tie should be broken in favor of Appellants and the rejection withdrawn, since the Examiner has not established a prima facie case for a rejection for lack of utility.

Nevertheless, Appellants have in fact submitted (on February 10, 2003) a Declaration under 37 CFR § 1.132 by Dr. Yasumichi Hitoshi containing additional data that confirms the use of the 2.2412 protein as a tumor marker. Dr. Hitoshi declared that at least two publications have associated 2.2412 expression with human cancers. Specifically, 2.2412 has been reported to be a tumor-specific antigen as evidenced by detection of 2.2412 antibodies in sera of breast cancer patients[3] and in sera of patients having meningioma.[4]

Furthermore, Dr. Hitoshi declared that it in his opinion a person having ordinary skill in the art reading the instant application at the time of the filing thereof would have found the assertion that 2.2412 is a tumor marker to be credible. In addition, Dr. Hitoshi declared further that the additional data submitted in the declaration further support the assertion in the instant application that the 2.2412 protein and its encoding polynucleotide are useful as a tumor marker.

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[3] Kuimov et al., 2001 Genes Immun. 2:52-5.
[4] Monz et al., 2001 Clin. Cancer Res. 7:113-9.

The Hitoshi declaration is further extrinsic evidence that substantiates Appellants' statement of utility. It is improper to dismiss summarily the contents of this declaration because they were not part of the specification as filed (see above).

After discussing *Fisher* in the Final Office Action, the Examiner made an unsupported statement that "detection of an isolated polynucleotide molecule of SEQ ID NO:1 or the encoded polypeptide of SEQ ID NO: 2 provides no information regarding presence or absence of any pathological condition, including breast or other form of cancer." First, such a statement does not break the 50-50 tie; it is but another example of the Examiner's unsupported opinion, which is contrary to the evidence of record. Second, the statement is not relevant to each of Appellants' utilities delineated above. Appellants reiterate that to satisfy the utility requirement an applicant need only provide one credible assertion of specific and substantial utility for each claimed invention. MPEP § 2107.

Appellants submit that the *Fisher* case is one dealing with ESTs. The court in *Fisher* held that "the claimed ESTs are, in words of the Supreme Court, mere 'object[s] of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *Fisher* at 1373 (citation omitted). Unlike in *Fisher*, Appellants' utility statement is supported by evidence which would lead one of ordinary skill in the art to consider Appellants' utility statement credible as well as specific and substantial. However, to the extent that the *Fisher* court stated that the utility threshold is not high (both the applicant and the solicitor agreed to this), it is very much on point. *Fisher* at 1370.

Appellants respectfully request withdrawal of this rejection.

Procedural Flaws in the § 101 Rejection

The Examiner rejected the claims under 35 U.S.C. § 101 "because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility...." It is unclear from this statement whether the Examiner considers Appellants' utilities 1) credible but not specific and substantial or 2) specific and substantial but not credible. Appellants have requested clarification

from the Examiner, but have received none. Accordingly, the statement of the rejection remains unclear.

The phrasing of the rejection is contrary to the Utility Guidelines, contrary to the MPEP at § 2107 II(C), and even contrary to *In re Fisher*, *supra*, cited by the Examiner. In *Fisher*, the government contended "that a patent applicant need disclose only a single specific and substantial utility ... the very standard articulated in the PTO's 'Utility Examination Guidelines' ... and followed here when examining the ... application." *Fisher* at 1370. It should be noted that the court did not say single specific and substantial credible utility (i.e. the court did not employ the phraseology used by the Examiner in the instant Final Rejection). Based on the court's language, it is apparent that the court and PTO considered Fisher's utility credible, but not specific and substantial. However, the phrasing of the present rejection does not permit one to understand (as in *Fisher*) whether the Examiner considers the utility credible, but not specific and substantial because all three terms (*credible*, *specific*, and *substantial*) appear in the statement of the rejection. The Utility Guidelines provide for a rejection for no specific and substantial utility, and they provide for a rejection for no credible utilty. The Guidelines do not provide for a rejection for no specific and substantial credible utility.

The Examiner cited MPEP § 2107 II(B) in response to Appellants request for clarification, but MPEP § 2107 II(C) would appear to control over MPEP § 2107 II(B), since MPEP § 2107 II(C) discusses how to make (phrase) the rejection. MPEP § 2107 II(C) provides for two rejection situations: (1) where the asserted utility is *not* specific or substantial, and (2) where the asserted utility *is* specific and substantial, but is not credible. In situation (1), the issue of credibility is not reached in the rejection. In situation (2), the only basis for rejection is lack of credibility. Therefore, MPEP § 2107 II(C) does not provide for a rejection under 35 U.S.C. § 101 for lacking an apparent or disclosed specific and substantial credible utility, i.e., it does not provide for the phraseology employed by the Examiner.

II. In summary, the enablement ("how to use") rejection under 35 U.S.C. § 112, first paragraph is based on the Examiner's allegation that one would not know

how to use the claimed invention because allegedly it is not supported by either a clear asserted utility or a well established utility for reasons set forth in the rejection under 35 U.S.C. § 101.

Appellants reiterate their arguments above. Because the § 101 rejection is flawed for the reasons set forth above, the enablement rejection must fall. Appellants respectfully request withdrawal of this rejection.

SUMMARY

Claims 5-7, 19-22, 24-29, and 31-41 are not unpatentable under 35 U.S.C. §§ 101 and 112, first paragraph. Appellants' specification discloses at least two utilities that are credible and more likely than not specific and substantial. Therefore, rejections for lack of utility and enablement are improper.

RELIEF REQUESTED

The Appellants respectfully request that the rejection of under 35 U.S.C. §§ 101 and 112, first paragraph be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: June 28, 2006 By: _____

Richard A. Schwartz
Registration No. 48,105

Date: June 28, 2006 By: _____

Carol L. Francis
Registration No. 36,513

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Claims Appendix

5. A host cell transformed with the polynucleotide molecule of claim 32.

6. The host cell of claim 5, wherein the host cell is a mammalian, insect, yeast or bacterial host cell.

7. A method of producing a protein, comprising culturing the host cell of claim 5 under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein.

19. An isolated polynucleotide molecule according to claim 32, wherein the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1.

20. A vector comprising a polynucleotide molecule according to claim 32.

21. A vector according to claim 20, wherein the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1.

22. An isolated polynucleotide molecule comprising a nucleotide sequence having at least 95% sequence identity to that shown in SEQ ID NO:1.

24. A host cell transformed with the polynucleotide molecule of claim 22.

25. The host cell of claim 24, wherein the host cell is a mammalian, insect, yeast or bacterial host cell.

26. A method of producing a protein, comprising culturing the host cell of claim 24 under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein.

27. An isolated polynucleotide molecule according to claim 22, wherein the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1.

28. A vector comprising a polynucleotide molecule according to claim 22.

29. A vector according to claim 28, wherein the polynucleotide molecule comprises a nucleotide sequence as shown in SEQ ID NO:1.

31. A polynucleotide according to claim 32, wherein the polynucleotide molecule comprises a nucleotide sequence encoding an amino acid sequence as shown in SEQ ID NO:2.

32. An isolated polynucleotide molecule comprising a nucleotide sequence having at least 95% sequence identity to a nucleotide sequence encoding SEQ ID NO:2.

33. An isolated polynucleotide molecule comprising a nucleotide sequence having at least 95% sequence identity to a nucleotide sequence encoding amino acid residues 232-538 of SEQ ID NO:2.

34. A host cell transformed with the polynucleotide molecule of claim 33.

35. The host cell of claim 34, wherein the host cell is a mammalian, insect, yeast or bacterial host cell.

36. A method of producing a polypeptide, comprising culturing the host cell of claim 34 under conditions suitable for the expression of the polynucleotide molecule and optionally recovering the protein.

37. An isolated polynucleotide molecule according to claim 33, wherein the nucleotide sequence comprises a nucleotides sequence of nucleotides 694-1614 of SEQ ID NO:1.

38. A vector comprising a polynucleotide molecule according to claim 33.

39. A vector according to claim 38, wherein the polynucleotide comprises a nucleotides sequence of nucleotides 694-1614 of SEQ ID NO:1.

40. The isolated polynucleotide molecule according to claim 33, wherein the polynucleotide molecule comprises a nucleotide sequence encoding amino acid residues 232-538 of SEQ ID NO:2.

41. The isolated polynucleotide molecule according to claim 33, wherein the polynucleotide molecule comprises a nucleotide sequence encoding amino acid residues 232-888 of SEQ ID NO:2.

EVIDENCE APPENDIX

No evidence submitted under 37 CFR §§ 1.130 or 1.131 has been relied upon by Appellants in this Appeal. Appellants rely upon the Declaration of Dr. Yasumichi Hitoshi under 37 CFR §1.132, originally filed on February 10, 2003, a copy of which is attached hereto.

RELATED PROCEEDINGS APPENDIX

There are no decisions rendered by a court or the Board which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

Atty Dkt. No.: RICE012
USSN: 09/509,196

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.
Typed or Printed Name Steven Goldstein
Signature [signature] Date 2/3/03

DECLARATION OF YASUMICHI HITOSHI UNDER 37 C.F.R. § 1.132 Address to: Assistant Commissioner for Patents Washington, D.C. 20231	Attorney Docket Confirmation No.	RICE-012 8868
	First Named Inventor	Roger John Daly
	Application Number	09/509,196
	Filing Date	March 23, 2000
	Group Art Unit	1646
	Examiner Name	Olga N. Chernyshev
	Title	"Potential Effector for the GRB7 Family of Signalling Proteins"

Dear Sir:

1. I, Yasumichi Hitoshi, M.D., Ph.D. declare and say I am a resident of the U.S.A. My residence address is 331 Callippe Court, Brisbane, CA 94005.

2. I hold a M.D. degree, which I received from Kumamoto University Medical School in 1987. I further hold a Ph.D. degree which I received from Kumamoto University Medical School in 1991. I am an expert in the fields of oncology research, retroviral technology, and cell cycle regulation. A copy of my curriculum vitae is attached as Exhibit 1.

3. I am currently hold the position of Associate Director at Rigel Pharmaceuticals, Inc.

4. I have read both the specificationof U.S. patent application serial no. 09/509,196(the '196 application) and the Office Action dated November 5, 2002 issued by the Examinerin this same patent application.

5. I understand that the pending claims are directed to a polynucleotide encoding the protein 2.2412, which is now referred to in the literature as Tankyrase2 or TaHo (Tankyrase Homolog), as well as vectors and host cells containing this polynucleotide, and use of this polynucleotide to produce the encoded 2.2412 protein.

6. I understand that the Patent Office has rejected all pending claims on the basis that the utility asserted in the '196 application is not credible. I further understand that the asserted utility disputed by the Patent Office is the use of 2.2412-encoding polynucleotide or 2.2412 protein as a tumor marker.

Review of the '196 Application

7. The '196 application sets out the following statements (page and line numbers in brackets refer to the specific parts of the '196 application::

a) **2.2412 protein is an effector protein for the Grb7 family of signalling proteins** (a protein that specifically binds to a signaling protein to facilitate a signal transduction cascade)
   i) **2.2412 protein specifically binds Grb14 and specifically binds Grb7** (page 10, line 26 to page 11, line 32)
   ii) **binding of 2.2412 protein to Grb14 requires the N-terminal region of Grb14, which contains highly conserved proline-rich motif thought to mediates interaction of the Grb7 family of proteins with their effectors** (page 11, lines 29-32)
   iii) **2.2412 contains multiple ankyrin repeats, which are known to have a role in protein-protein interactions** (page 9, lines 25-34)

b) **Grb7 family members are signal transduction molecules that exhibit differential expression in certain human cancers (particularly breast cancer)** (page 5, lines 13-15). Specifically, at the time of filing

i) Grb7 family members were known to be associated with oesophageal carcinoma,[1] primary gastric cancer,[2] and breast cancer.[3]

ii) **Grb14 was known to be differentially expressed in breast cancer**[4]

iii) **Grb7 was known to be differentially expressed in breast cancer**[5]

8. Given that 2.2412 specifically binds Grb14 and specifically binds Grb7, each which were known at the time the application was filed (September 23, 1997) to be differentially expressed in cancer cells compared to normal cells, it is reasonable to conclude that effectors for these proteins such as 2.2412 will also be differentially expressed (specification page 5, lines 13-16).

9. In my opinion, the '196 application sets out a credible association of 2.2412 expression and human cancers.

10. This association of 2.2412 expression with human cancers has been further supported in at least two publications. Specifically, 2.2412 (also known as Tankyrase2[6]) has been reported to be a tumor-specific antigen as evidenced by detection of anti-Tankyerase2 antibodies in sera of breast cancer patients[7] and in sera of patients having meningioma.[8]

---

[1] Tanaka et al. 1997 Cancer Res. 57:28-31.
[2] Kishi et al. 1997 Biochem Biophys. Res. Commn. 232:5-9.
[3] Stein et al. 1994 EMBO J 13:1331-40.
[4] Daly et al. 1996 J. Biol. Chem 271:12502-10.
[5] Stein et al. 1994 EMBO J 13:1331-40
[6] Lyons et al. 2001 J. Biol. Chem. 276:17172-80.
[7] Kuimov et al., 2001 Genes Immun. 2:52-5.
[8] Monz et al., 2001 Clin. Cancer Res. 7:113-9.

11. In summary, after reviewing the '196 application, it is my opinion that a person having ordinary skill reading the '196 application at the time the application was filed (September 23, 1997) would find the assertion that 2.2412 (Tankyrase2) is a tumor marker to be credible in view of the disclosure in the specification as set out above.

Additional Data Confirming the Use of 2.2412 as a Tumor Marker

12. In my position at Rigel Pharmaceuticals, Inc., I have directed others and personally performed research to examine the expression of 2.2412 (also referred to as Tankyrase2 or Tankyrase Homologue (TaHo)) in both normal and cancerous human cells.

13. Expression of 2.2412 was examined using a Taqman Assay. Matched tumor and normal cDNAs from lung and breast tissue were obtained from two different sources: BioChain Inc. and Clontech (clinical histories of Clontech cDNAs were not available). Location of the primers within the 2.2412 (TaHo) sequence are indicated as bolded and underlined sequences in Exhibit 2. In addition, the TaHo sequence was aligned with the Tankyrase sequence in order to demonstrate the specificity of the Taqman analysis using these primers for Tankyrase homologue. Analysis was done in triplicate and standard errors for normal and tumor tissue were determined. Expression levels in the matched samples were normalized to Ribosomal Protein S9 (S9) and the 23kD Highly Basic Protein (HBP).

14. The results of these studies are shown in Exhibit 3. As shown in the graphs, 2.2412 is expressed at significantly higher levels in two types of lung cancer (bronchioalveolar carcinoma and large cell carcinoma) relative to normal lung tissue. 2.2412 is also expressed at significantly higher levels in three types of breast cancer (invasive ductal carcinoma, intraductal carcinoma and invasive lobular carcinoma) compare to normal breast tissue.

15. These data further support the assertion in the '196 application that the 2.2412 protein and its encoding polynucleotide are useful as a tumor marker.

16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such will false statements may jeopardize the validity of the application or any patent issuing thereon.

2/3/03
Date

Yasumichi Hitoshi, Ph.D.

Attachments:

Exhibit 1: Curriculum vitae of Dr. Yasumichi Hitoshi
Exhibit 2: Primers used in expression analysis of 2.2412
Exhibit 3: Graphs showing expression of 2.2412 in normal and cancerous human cells

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EXHIBIT 1

Curriculum vitae

Name: Yasumichi Hitoshi, MD. Ph.D.

Born: November 21, 1961. Kumamoto, Japan

Citizenship: Japan

Present Position: Associate director, Project leader

Present address: Department of Cell Biology
Rigel pharmaceutical Inc.,
240 East grand avenue,
CA 94081
U.S. A.
Telephone: 650-624-1128
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E-mail: yhitoshi@rigel.com

Professional experience:

2002.7-present Associate director, Project leader

Department of Department of Cell Biology,

Rigel pharmaceutical Inc.

Research:

2002.1-2002.7 Group leader, Project leader

Department of Department of Cell Biology,

Rigel pharmaceutical Inc.

Research:

1998.12-2001.12 Senior scientist, Project leader

Department of Department of Cell Biology,

Rigel pharmaceutical Inc.

Research: Identification of proteins and peptides that play an important role in cell cycle regulation of specific tumor cells using retroviral functional screens.

1998.2-1998.12 Senior scientist
Department of Department of Cell Biology,
Rigel pharmaceutical Inc.
Research: Characterization of a membrane receptor, Toso, which inhibit TNF receptor family-induced apoptosis.

1995.3-1998.2 Postdoctoral Fellow
Department of Molecular Pharmacology, Stanford University.
Research: Analysis of signaling pathway using high titer retrovirus.
Scientific Advisor: Assistant Professor Garry P. Nolan

1992.1-1995.3 Postgraduate Research Associate
Department of Immunology,
The Institute of Medical Science,
The University of Tokyo.
Scientific Advisor: Professor Kiyoshi Takatsu
Research: Cellular mechanism of development of a retrovirus-induced immunodeficiency syndrome (MAIDS)

1991.4-1991.12 Postgraduate Research Associate
Department of Biology,
The Institute for Medical Immunology,
Kumamoto University Medical School.
Scientific Advisor: Professor Kiyoshi Takatsu
Research: Signal transduction through IL-5 receptor and involvement of Xid defect in the receptor system.

Education:

Medical School

1981-1987 Kumamoto University Medical School

Graduate School

1987-1991 Department of Biology,
The Institute for Medical Science,
Kumamoto University Medical School
Research: Immunology
Scientific Advisor: Professor Kiyoshi Takatsu

Thesis Dissertation: Role of interleukin 5 and its receptor in the immune system.

Membership of learned societies:

Japanese Society of Immunology
Japanese Cancer Association

Honors and Fellowships

Special Fellow of The Japanese Ministry of Education, Culture and Science, April 1990-March 1991.

The Uehara Memorial Foundation Fellowship, April 1995-March 1996.

Publications

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Patent

1. Toso, a cell-surface specific regulator of Fas-induced apoptosis in T cells
   Stanford Docket S98-019

Exhibit 2

Primers for TaHo Experiment

Forward primer	Reverse primer	Fluorescent probe
CGGATGATGTCAGCGCTCTT	CCTGGGCTTCTCACACCATT	CCCCCATCTGCTCTGCCCTCTTG

Thermal Cycle Conditions

Cycle	Temperature	Time	Repeat
Hold	50 C	2 min	
Hold	95 C	10 min	
Cycle	95 C	15 sec.	40 cycle
	60 C	1 min.	

Alignment of DNA sequences of 2.2412 (Tankyrse2 or TaHo) and Tankyrase by CLUSTAL W (1.8) multiple sequence alignment.
Sequences in bold and underline show sequence of 2.2412 forward primer.
* indicates identify of sequence of 2.2412 (Tankyrase2) and Tankyrase.

```
Tankyrase2      ------------------------------------------------------------
Tankyrase       ATGGCGGCGTCGCGTCGCTCTCAGCATCATCACCACCATCATCAACAACAGCTCCAGCCC

Tankyrase2      ------------------------------------------------------------
Tankyrase       GCCCCAGGGGCTTCAGCGCCGCCGCCGCCACCTCCTCCCCCACTCAGCCCTGGCCTGGCC

Tankyrase2      ------------------------------------------------------------
Tankyrase       CCGGGGACCACCCCAGCCTCTCCCACGGCCAGCGGCCTGGCCCCCTTCGCCTCCCCGCGG

Tankyrase2      ------------------------------------------------------------
Tankyrase       CACGGCCTAGCGCTGCCGGAGGGGGATGGCAGTCGGGATCCGCCCGACAGGCCCCGATCC

Tankyrase2      ------------------------------------------------------------
Tankyrase       CCGGACCCGGTTGACGGTACCAGCTGTTGCAGTACCACCAGCACAATCTGTACCGTCGCC

Tankyrase2      ------------------------------------------------------------
Tankyrase       GCCGCTCCCGTGGTCCCAGCGGTTTCTACTTCATCTGCCGCTGGGGTCGCTCCCAACCCA

Tankyrase2      ------------------------------------------------------------
Tankyrase       GCCGGCAGTGGCAGTAACAATTCACCGTCGTCCTCTTCTTCCCCGACTTCTTCCTCATCT

Tankyrase2      ------------------------------------------------------ATGTCGG
Tankyrase       TCCTCTCCATCCTCCCCTGGATCGAGCTTGGCGGAGAGCCCCGAGGCGGCCGGAGTTAGC
                                                                      *  * *

Tankyrase2      GTCGCCGCTGCGCCGGCGGG-GGAGCGGCCTGCGCGAGCGCCGCGGCCGAGGCCGTGGAG
Tankyrase       AGCACAGCACCACTGGGGCCTGGGGCAGCAGGACCTGGGACAGGGGTCCCAGCAGTGAGC
                  * * **  * * ** *   ** ** **  *  *  *  * * ** *   ** ***

Tankyrase2      CCGGCCGCCCGAGAGCTGTTCGAGGCGTGCCGCAACGGGGACGTGGAACGAGTCAAGAGG
Tankyrase       GGGGCCCTACGGGAACTGCTGGAGGCCTGTCGCAATGGGGACGTGTCCCGGGTAAAGAGG
                  ****   ** ** *** * ***** ** ***** *********   ** ** ******
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Tankyrase2      CTGGTGACGCCTGAGAAGGTGAACAGCCGCGACACGGCGGGCAGGAAATCCACCCCGCTG
Tankyrase       CTGGTGGACGCGGCAAACGTAAATGCAAAGGACATGGCCGGCCGGAAGTCTTCTCCCCTG
                ******    * *  ** ** **       **** *** *** **** **  * ** ***

Tankyrase2      CACTTCGCCGCAGGTTTTGGGCGGAAAGACGTAGTTGAATATTTGCTTCAGAATGGTGCA
Tankyrase       CACTTCGCTGCAGGTTTTGGAAGGAAGGATGTTGTAGAACACTTACTACAGATGGGTGCT
                ******** ***********  **** ** ** ** *** * ** ** ****  *****

Tankyrase2      AATGTCCAAGCACGTGATGATGGGGGCCTTATTCCTCTTCATAATGCATGCTCTTTTGGT
Tankyrase       AATGTCCACGCTCGTGATGATGGAGGTCTCATCCCGCTTCATAATGCCTGTTCTTTTGGC
                ******** ** ********** ** ** ** ** ********** ** ********

Tankyrase2      CATGCTGAAGTAGTCAATCTCCTTTTGCGACATGGTGCAGACCCCAATGCTCGAGATAAT
Tankyrase       CATGCTGAGGTTGTGAGTCTGTTATTGTGCCAAGGAGCTGATCCAAATGCCAGGGATAAC
                ******** ** ** * ***  * *** * ** ** ** ** ** *****  * *****

Tankyrase2      TGGAATTATACTCCTCTCCATGAAGCTGCAATTAAAGGAAAGATTGATGTTTGCATTGTG
Tankyrase       TGGAACTATACACCTCTGCATGAAGCTGCTATTAAAGGGAAGATCGATGTGTGCATTGTG
                ***** ***** ***** ********** ******** ***** ***** *********

Tankyrase2      CTGTTACAGCATGGAGCTGAGCCAACCATCCGAAATACAGATGGAAGGACAGCATTGGAT
Tankyrase       CTGCTGCAGCACGGAGCTGACCCAAACATTCGGAACACTGATGGGAAATCAGCCCTGGAC
                *** * ***** ******** **** *** ** ** ** ***** *   ****  ****

Tankyrase2      TTAGCAGATCCATCTGCCAAAGCAGTGCTTACTGGTGAATATAAGAAAGATGAACTCTTA
Tankyrase       CTGGCAGATCCTTCAGCAAAAGCTGTCCTTACAGGTGAATACAAGAAAGACGAACTCCTA
                 * ******** ** ** ***** ** ***** ******** ******** ****** **

Tankyrase2      GAAAGTGCCAGGAGTGGCAATGAAGAAAAAATGATGGCTCTACTCACACCATTAAATGTC
Tankyrase       GAAGCTGCTAGGAGTGGTAATGAAGAAAAACTAATGGCTTTACTGACTCCTCTAAATGTG
                ***  *** ******** ********** * ****** **** ** **  *******

Tankyrase2      AACTGCCACGCAAGTGATGGCAGAAAGTCAACTCCATTACATTTGGCAGCAGGATATAAC
Tankyrase       AATTGCCATGCAAGTGATGGGCGAAAGTCGACTCCTTTACATCTAGCAGCGGGCTACAAC
                ** ***** **********  ******* ***** ****** * ***** ** ** ***

Tankyrase2      AGAGTAAAGATTGTACAGCTGTTACTGCAACATGGAGCTGATGTCCATGCTAAAGATAAA
Tankyrase       AGAGTTCGAATAGTTCAGCTTCTTCTTCAGCATGGTGCTGATGTTCATGCAAAAGACAAA
                *****    ** ** *****  * ** ** ***** ******** ***** ***** ***

Tankyrase2      GGTGATCTGGTACCATTACACAATGCCTGTTCTTATGGTCATTATGAAGTAACTGAACTT
Tankyrase       GGTGGACTTGTGCCTCTTCATAATGCATGTTCATATGGACATTATGAAGTCACAGAACTG
                ****  ** ** **  * ** ***** ***** ***** ********** ** *****

Tankyrase2      TTGGTCAAGCATGGTGCCTGTGTAAATGCAATGGACTTGTGGCAATTCACTCCTCTTCAT
Tankyrase       CTACTAAAGCATGGAGCTTGTGTTAATGCCATGGATCTCTGGCAGTTTACTCCACTGCAC
                 *  * ******** ** ***** ***** *****  * ***** ** ***** ** **

Tankyrase2      GAGGCAGCTTCTAAGAACAGGGTTGAAGTATGTTCTCTTCTCTTAAGTTATGGTGCAGAC
Tankyrase       GAGGCTGCTTCCAAGAACCGTGTAGAAGTCTGCTCTTTGTTACTTAGCCATGGCGCTGAT
                ***** ***** ****** * ** ***** ** *** *  *  * **  **** ** **
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```
Tankyrase2      CCAACACTGCTCAATTGTCACAATAAAAGTGCTATAGACTTGGCTCCCACACCACAGTTA
Tankyrase       CCTACGTTAGTCAACTGCCATGGCAAAAGTGCTGTGGATATGGCTCCAACTCCGGAGCTT
                ** **  *  **** ** **    ********* * **  ******* ** **  ** *

Tankyrase2      AAAGAAAGATTAGCATATGAATTTAAAGGCCACTCGTTGCTGCAAGCTGCACGAGAAGCT
Tankyrase       AGGGAGAGATTGACTTATGAATTTAAAGGTCATTCTTTACTACAAGCAGCCAGAGAAGCA
                *  ** *****  * ************** ** ** ** ** ***** **  *******

Tankyrase2      GATGTTACTCGAATCAAAAAACATCTCTCTCTGGAAATGGTGAATTTCAAGCATCCTCAA
Tankyrase       GACTTAGCTAAAGTTAAAAAAACACTCGCTCTGGAAATCATTAATTTCAAACAACCGCAG
                **  *  **  * * ******   *** **********  * ******** ** ** **

Tankyrase2      ACACATGAAACAGCATTGCATTGTGCTGCTGCATCTCCATATCCCAAAAGAAAGCAAATA
Tankyrase       TCTCATGAAACAGCACTGCACTGTGCTGTGGCCTCTCTGCATCCCAAACGTAAACAAGTG
                 * ************ **** *******  ** ****   ******** * ** *** *

Tankyrase2      TGTGAACTGTTGCTAAGAAAAGGAGCAAACATCAATGAAAAGACTAAAGAATTCTTGACT
Tankyrase       ACAGAATTGTTACTTAGAAAAGGAGCAAATGTTAATGAAAAAAATAAAGATTTCATGACT
                   *** **** ** **************  * ******** * ****** *** *****

Tankyrase2      CCTCTGCACGTGGCATCTGAGAAAGCTCATAATGATGTTGTTGAAGTAGTGGTGAAACAT
Tankyrase       CCCCTGCATGTTGCAGCCGAAAGAGCCCATAATGATGTCATGGAAGTTCTGCATAAGCAT
                ** ***** ** *** * ** * *** ***********  * *****  **   ** ***

Tankyrase2      GAAGCAAAGGTTAATGCTCTGGATAATCTTGGTCAGACTTCTCTACACAGAGCTGCATAT
Tankyrase       GGCGCCAAGATGAATGCACTGGACACCCTTGGTCAGACTGCTTTGCATAGAGCCGCCCTA
                *  ** *** * ***** ***** *  ************ ** * ** ***** **

Tankyrase2      TGTGGTCATCTACAAACCTGCCGCCTACTCCTGAGCTATGGGTGTGATCCTAACATTATA
Tankyrase       GCAGGCCACCTGCAGACCTGCCGCCTCCTGCTGAGTTACGGCTCTGACCCCTCCATCATC
                   ** ** ** ** *********** ** ***** ** ** * *** **   *** **

Tankyrase2      TCCCTTCAGGGCTTTACTGCTTTACAGATGGGAAATGAAAATGTACAGCAACTCCTCCAA
Tankyrase       TCCTTACAAGGCTTCACAGCAGCACAGATGGGCAATGAAGCAGTGCAGCAGATTCTGAGT
                *** * ** ***** ** **   ********* ******   ** *****  * **

Tankyrase2      GAGGGTATCTCATTAGGTAATTCAGAGGCAGACAGACAATTGCTGGAAGCTGCAAAGGCT
Tankyrase       GAGAGTACACCTATACGTACTTCTGATGTTGATTATCGACTCTTAGAGGCATCTAAAGCT
                *** ***   *  ** *** *** ** *  **    * * *  * ** **  * ** ***

Tankyrase2      GGAGATGTCGAAACTGTAAAAAAACTGTGTACTGTTCAGAGTGTCAACTGCAGAGACATT
Tankyrase       GGAGACTTGGAAACTGTGAAGCAACTTTGCAGCTCTCAAAATGTGAATTGTAGAGACTTA
                *****  * ******** **  **** ** *    *** * *** ** ** ****** *

Tankyrase2      GAAGGGCGTCAGTCTACACCACTTCATTTTGCAGCTGGGTATAACAGAGTGTCCGTGGTG
Tankyrase       GAGGGCCGGCATTCCACGCCCTTACACTTCGCAGCAGGCTACAACCGCGTGTCTGTTGTA
                ** ** ** ** ** ** **  * ** ** ***** ** ** *** * ***** ** **

Tankyrase2      GAATATCTGCTACAGCATGGAGCTGATGTGCATGCTAAAGATAAAGGAGGCCTTGTACCT
Tankyrase       GAGTACCTGCTACACCACGGTGCCGATGTCCATGCCAAAGACAAGGGTGGCTTGGTGCCC
                ** ** ******** ** ** ** ***** ***** ***** ** ** *** * ** **
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Tankyrase2      TTGCACAATGCATGTTCTTATGGACATTATGAAGTTGCAGAACTTCTTGTTAAACATGGA
Tankyrase       CTTCATAATGCCTGTTCATATGGACACTATGAGGTGGCTGAGCTTTTAGTAAGGCATGGG
                 * ** ***** ***** ******** ***** ** ** ** *** * ** *  *****

Tankyrase2      GCAGTAGTTAATGTAGCTGATTTATGGAAATTTACACCTTTACATGAAGCAGCAGCAAAA
Tankyrase       GCTTCTGTCAATGTGGCGGACTTATGGAAATTTACCCCTCTCCATGAAGCAGCAGCTAAA
                **    ** ***** ** ** ************** *** * ************** ***

Tankyrase2      GGAAAATATGAAATTTGCAAACTTCTGCTCCAGCATGGTGCAGACCCTACAAAAAAAAAC
Tankyrase       GGAAAGTATGAAATCTGCAAGCTCCTTTTAAAACATGGAGCAGATCCAACTAAAAAGAAC
                ***** ******** ***** ** **  *  * ***** ***** ** ** ***** ***

Tankyrase2      AGGGATGGAAATACTCCTTTGGATCTTGTTAAAGATGGAGATACAGATATTCAAGATCTG
Tankyrase       AGAGATGGAAATACACCTTTGGATTTGGTAAAGGAAGGAGACACAGATATTCAGGACTTA
                ** *********** ********* * ** ** ** ***** ********** **  *

Tankyrase2      CTTAGGGGAGATGCAGCTTTGCTAGATGCTGCCAAGAAGGGTTGTTTAGCCAGAGTGAAG
Tankyrase       CTGAAAGGGGATGCTGCTTTGTTGGATGCTGCCAAGAAGGGCTGCCTGGCAAGAGTGCAG
                ** *  ** ***** ****** * ***************** **  * ** ****** **

Tankyrase2      AAGTTGTCTTCTCCTGATAATGTAAATTGCCGCGATACCCAAGGCAGACATTCAACACCT
Tankyrase       AAGCTCTGTACCCCAGAGAATATCAACTGCAGAGACACCCAGGGCAGAAATTCAACCCCT
                *** * * * * ** ** *** * ** *** * ** ***** ****** ******* ***

Tankyrase2      TTACATTTAGCAGCTGGTTATAATAATTTAGAAGTTGCAGAGTATTTGTTACAACACGGA
Tankyrase       CTGCACCTGGCAGCAGGCTATAATAACCTGGAAGTAGCTGAATATCTTCTAGAGCATGGA
                 * **  * ***** ** ********  * ***** ** ** *** *  ** * ** ***

Tankyrase2      GCTGATGTGAATGCCCAAGACAAAGGAGGACTTATTCCTTTACATAATGCAGCATCTTAC
Tankyrase       GCTGATGTTAATGCCCAGGACAAGGGTGGTTTAATTCCTCTTCATAATGCGGCATCTTAT
                ******** ******** ***** ** **  * ****** * ******** ********

Tankyrase2      GGGCATGTAGATGTAGCAGCTCTACTAATAAAGTATAATGCATGTGTCAATGCCACGGAC
Tankyrase       GGGCATGTTGACATAGCGGCTTTATTGATAAAATACAACACGTGTGTAAATGCAACAGAT
                ******** **  **** *** ** * ***** ** **  * ***** ***** ** **

Tankyrase2      AAATGGGCTTTCACACCTTTGCACGAAGCAGCCCAAAAGGGACGAACACAGCTTTGTGCT
Tankyrase       AAGTGGGCGTTTACTCCCCTCCATGAAGCAGCCCAGAAAGGAAGGACGCAGCTGTGCGCC
                ** ***** ** ** **  * ** *********** ** *** * ** ***** ** **

Tankyrase2      TTGTTGCTAGCCCATGGAGCTGACCCGACTCTTAAAAATCAGGAAGGACAAACACCTTTA
Tankyrase       CTCCTCCTAGCGCATGGTGCAGACCCCACCATGAAGAACCAGGAAGGCCAGACGCCTCTG
                 *  * ***** ***** ** ***** **  * ** ** ******** ** ** *** *

                              Forward Primer                          Fluorescent
Tankyrase2      GATTTAGTTTCAGCGGATGATGTCAGCGCTCTTCTGACAGCAGCCATGCCCCCATCTGCT
Tankyrase       GATCTGGCAACAGCTGACGATATCAGAGCTTTGCTGATAGATGCCATGCCCCCAGAGGCC
                *** * *   **** ** *** **** *** * **** **  ************   **

                probe                              Reverse primer
Tankyrase2      CTGCCCTCTTGTTACAAGCCTCAAGTGCTCAATGGTGTGAGAAGCCCAGGAGCCACTGCA
Tankyrase       TTACCTACCTGTTTTAAACCTCAGGC--T-ACTGTAGTGAG----T-----GCCTCTCTG
                 * **  * ****  ** ***** *   * * **  *****          *** **
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Tankyrase2      GATGCTCTCTCTTCAGGTCCATCTAGCCCATCAAGCCTTTCTGCAGCCAGCAGTCTTGAC
Tankyrase       A------TCTCACCAG---CATCCACCCCCTCCTGCCTCTCGGCTGCCAGCAGCATAGAC
                      ****  ***   **** * *** **  **** ** ** ********  * ***

Tankyrase2      AACTTATCTGGGAGTTTTTCAGAACTGTCTTCAGTAGTTAGTTCAAGTGGAACAGAGGGT
Tankyrase       AACCTCACTGGCCCTTTAGCAGAGTTGGCCGTAGGAGGAGCCTCCAATGCAGGGGATGGC
                *** *  ****   ***  ****  ** *   ** **     ** * ** *   ** **

Tankyrase2      GCTTCCAGTTTGGAGAAAAAGGAGGTTCCAGGAGTAGATTTTAGCATAACT------CAA
Tankyrase       GCCGCGGGAACAGAAAGGAAGGAAGGAGAAGTTGCTGGTCTTGACATGAATATCAGCCAA
                **  *  *    ** *  ***** *    **  *  * * **  *** * *      ***

Tankyrase2      TTCGTAAGGAATCTTGGACTTGAGCACCTAATGGATATATTTGAGAGAGAACAGATCACT
Tankyrase       TTTCTAAAAAGCCTTGGCCTTGAACACCTTCGGGATATCTTTGAAACAGAACAGATTACA
                **  ***  *  ***** ***** *****   ****** ***** * ********* **

Tankyrase2      TTGGATGTATTAGTTGAGATGGGGCACAAGGAGCTGAAGGAGATTGGAATCAATGCTTAT
Tankyrase       CTAGATGTGTTGGCTGATATGGGTCATGAAGAGTTGAAAGAAATAGGCATCAATGCATAT
                 * ***** ** * *** ***** **  * *** **** ** ** ** ******** ***

Tankyrase2      GGACATAGGCACAAACTAATTAAAGGAGTCGAGAGACTTATCTCCGGACAACAAGGTCTT
Tankyrase       GGGCACCGCCACAAATTAATCAAAGGAGTAGAAAGACTCTTAGGTGGACAACAAGGCACC
                ** **  * ****** **** ******** ** *****  *    ***********

Tankyrase2      AACCCATATTTAACTTTGAACACCTCTGGTAGTGGAACAATTCTTATAGATCTGTCTCCT
Tankyrase       AATCCTTATTTGACTTTTCACTGTGTTAATCAGGGAACGATTTTGCTGGATCTTGCTCCA
                ** ** ***** *****  **     *  *   ***** *** *  * *****  ****

Tankyrase2      GATGATAAAGAGTTTCAGTCTGTGGAGGAAGAGATGCAAAGTACAGTTCGAGAGCACAGA
Tankyrase       GAAGATAAAGAATATCAGTCAGTGGAAGAAGAGATGCAAAGTACTATTCGAGAACACAGA
                ** ******** * ****** ***** ****************  ******* ******

Tankyrase2      GATGGAGGTCATGCAGGTGGAATCTTCAACAGATACAATATTCTCAAGATTCAGAAGGTT
Tankyrase       GATGGTGGTAATGCTGGCGGCATCTTCAACAGATACAATGTCATTCGAATTCAAAAAGTT
                ***** *** **** ** ** ****************** *  *    ***** ** ***

Tankyrase2      TGTAACAAGAAACTATGGGAAAGATACACTCACCGGAGAAAAGAAGTTTCTGAAGAAAAC
Tankyrase       GTCAACAAGAAGTTGAGGGAGCGGTTCTGCCACCGACAGAAGGAAGTGTCTGAGGAGAAT
                   ********  *  ****  * * *   *****    ** ***** ***** ** **

Tankyrase2      CACAACCATGCCAATGAACGAATGCTATTTCATGGGTCTCCTTTTGTGAATGCAATTATC
Tankyrase       CACAACCATCACAATGAGCGCATGTTGTTTCATGGTTCTCCTTTCATTAATGCCATTATT
                *********  ****** ** *** * ******** ********  * ***** *****

Tankyrase2      CACAAAGGCTTTGATGAAAGGCATGCGTACATAGGTGGTATGTTTGGAGCTGGCATTTAT
Tankyrase       CATAAAGGGTTTGATGAGCGACATGCATACATAGGAGGAATGTTTGGGGCCGGGATTTAT
                ** ***** ********  * ***** ******** ** ******** ** ** ******

Tankyrase2      TTTGCTGAAAACTCTTCCAAAAGCAATCAATATGTATATGGAATTGGAGGAGGTACTGGG
Tankyrase       TTTGCTGAAAACTCCTCAAAAAGCAACCAATATGTTTATGGAATTGGAGGAGGAACAGGC
                ************** ** ******** ******** ***************** ** **
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Tankyrase2      TGTCCAGTTCACAAAGACAGATCTTGTTACATTTGCCACAGGCAGCTGCTCTTTTGCCGG
Tankyrase       TGCCCTACACACAAGGACAGGTCATGCTATATATGTCACAGACAAATGCTCTTCTGTAGA
                ** **    ***** ***** ** ** ** ** ** ***** **  ******* **  *

Tankyrase2      GTAACCTTGGGAAAGTCTTTCCTGCAGTTCAGTGCAATGAAAATGGCACATTCTCCTCCA
Tankyrase       GTGACCCTTGGGAAATCCTTTCTGCAGTTTAGCACCATGAAAATGGCCCACGCGCCTCCA
                ** *** * ** ** ** ** ******** **  * ********** **  * ******

Tankyrase2      GGTCATCACTCAGTCACTGGTAGGCCCAGTGTAAATGGCCTAGCATTAGCTGAATATGTT
Tankyrase       GGGCACCACTCAGTCATTGGTAGACCGAGCGTCAATGGGCTGGCATATGCTGAATATGTC
                ** ** ********** ****** ** ** ** ***** ** ****  **********

Tankyrase2      ATTTACAGAGGAGAACAGGCTTATCCTGAGTATTTAATTACTTACCAGATTATGAGGCCT
Tankyrase       ATCTACAGAGGAGAACAGGCATACCCAGAGTATCTTATCACTTACCAGATCATGAAGCCA
                ** ***************** ** ** ****** * ** ********** **** ***

Tankyrase2      GAAGGTATGGTCGATGG-ATAA----------------------
Tankyrase       GAAGCCCCTTCCCAGACCGCAACAGCCGCAGAGCAGAAGACCTAG
                ****       * *      **
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Exhibit 3: Expression Analysis of 2.2412 (Tankyrase2/Tankyrase Homologue) by Taqman Assay